Editorial Comment

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What do we mean by "mechanism" in pain medicine?

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The word "mechanism" has a positive connotation for scientists, and many of us who are pain clinicians deplore the lack of *mechanism-based* treatments. However, there seems to be a certain fuzziness concerning the word mechanism itself. What do we really mean when we use it? Of course, there are potentially deep philosophy-of-science issues here, not least in relation to the concept of causation [1]. My aim here is not to delve into these difficult issues, but just to superficially point out a few different uses of the word mechanism in the pain research community.

First, we have the concept of molecular mechanisms in cell biology. As expressed by Gardel: "The word mechanism in cell biology typically refers to a molecular mechanism that is explored rigorously by genetic and biochemical testing" [2]. It is about understanding how the "molecular machinery" works at cellular level. Second, there is the pharmacological/pharmacodynamical concept of mechanism of action for a certain drug. Although there is an obvious connection to molecular mechanisms, pharmacology is particularly concerned with downstream effects that occur after the interaction between drug and target. To take an obvious example, morphine binds to opioid receptors in the PAG (an event on the molecular level), and this elicits a response in the PAG-RVM system – in turn leading to analgesia. Here, we begin to see that the word mechanism can be used on a "supra-molecular" level as well. This becomes all the more evident with a third use, namely when pain clinicians talk about the triad nociceptive/neuropathic/nociplastic as three different pain mechanisms or "mechanistic descriptors" [3]. These are very general "descriptors" indeed and, from the perspective of molecular biology, one might wonder why the word mechanism is used at all in this context. However, it is important to realize that the word mechanism can be used on a system-wide physiological level – i.e., one can speak of *physiological* mechanisms. Kar & Saho express it as follows: "The mechanisms, by which the organ systems of the body function, are often referred to as 'physiological mechanisms'", and these "operate to maintain the homeostasis of the body" [4]. From that perspective, speaking of pathophysiological mechanisms does make sense – hence the use of the adjective mechanistic when talking about the trichotomy nociceptive/neuropathic/nociplastic.

Hopefully, clinicians are aware of the fact that the trichotomy is used as a heuristic. This is especially the case for the term "nociplastic". I think the situation here is analogous to what philosopher Churchland says about the definition of consciousness: "If we cannot begin with a solid definition, how do we get agreement on what phenomenon we are trying to study? Roughly, we use the same strategy here as we use in the early stages of any science: delineate the paradigm cases, and then try to bootstrap our way up from there. Using common sense, we begin by getting *provisional* agreement on what things count as *unproblematic* examples" [5]. Even though we cannot provide a precise definition of the term nociplastic (we are indeed in the "early stages" of pain science), I think we nonetheless have enough provisional agreement on paradigm cases, such as e.g. fibromyalgia. Undoubtedly, in the future, it will be shown that "nociplastic" was too broad a category and that it includes a range of more specific pathophysiological mechanisms. But for the time being, the term "nociplastic" is a useful provisional tool for describing pain from a certain point of view. Simply put: When pain is chronic, and neither associated with classical tissue damage nor with a lesion or disease of the somatosensory nervous system, we call it nociplastic. Or, to cite official IASP terminology: Nociplastic pain is pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Admittedly, this is a heuristic tool and not a precise definition, i.e., it mirrors reality only in a superficial and provisional manner. But at least we now have some

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kind of common language that we can use when we communicate about this broad and heterogenous group of patients. Needless to say, in the pain literature, the concept of physiological mechanisms is not only applied to the above-mentioned trichotomy. For instance, Mouraux et al. write about (among other things) "deficient descending control" [6] being a mechanism that can drive chronic pain states.

Fourth and very shortly, there is also the concept of *psychological* mechanisms. These have been defined as "the processes and systems, or activities and entities, frequently appealed to in causal explanations within the psychological sciences" [7]. Needless to say, this is also a very broad category.

Hence, when pain researchers speak about mechanisms, there are at least four different ways to understand what they mean. When a molecular biologist, a pharmacologist, a pain physician and a psychologist talk about "mechanisms", it seems to me they use the word in different ways and on different levels (from molecules to psychology). I therefore wonder if perhaps we should never just talk about mechanisms in general, i.e., may it be the case that we always should qualify our use of this concept?

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